Inotrope and vasopressor use in cardiogenic shock: what, when and why?

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Purpose of review
Despite increasing interest in the management of cardiogenic shock (CS), mortality rates remain unacceptably high. The mainstay of supportive treatment includes vasopressors and inotropes. These medications are recommended in international guidelines and are widely used despite limited evidence supporting safety and efficacy in CS.

Recent findings
The OptimaCC trial further supports that norepinephrine should continue to be the first-line vasopressor of choice in CS. The CAPITAL DOREMI trial found that milrinone is not superior to dobutamine in reducing morbidity and mortality in CS. Two studies currently underway will offer the first evidence of the necessity of inotrope therapy in placebo-controlled trials: CAPITAL DOREMI2 will randomize CS patients to inotrope or placebo in the initial resuscitation of shock to evaluate the efficacy of inotrope therapy and LevoHeartShock will examine the efficacy of levosimendan against placebo in early CS requiring vasopressor therapy.

Summary
Review of the current literature fails to show significant mortality benefit with any specific vasopressor or inotropic in CS patients. The upcoming DOREMI 2 and levosimendan versus placebo trials will further tackle the question of inotrope necessity in CS. At this time, inotrope selection should be guided by physician experience, availability, cost, and most importantly, individual patients' response to therapy.

Keywords
cardiogenic shock, inotrope, vasopressor

INTRODUCTION

Cardiogenic shock (CS) is a primary cardiac disorder of low cardiac output (CO) resulting in clinical and biochemical findings of end-organ hypoperfusion [1]. Pathophysiological changes include impaired myocardial contractility and reduced CO, associated with systemic vasoconstriction and coronary ischemia. The complex CS spiral can be worsened by concomitant systemic inflammation, vasodilation and abnormal nitric oxide handling. CS complicates approximately 5 to 10% of acute myocardial infarction (AMI) presentations [2]. Non-AMI etiologies of CS include acute decompensation of heart failure, severe valvular disease, arrhythmias and myocarditis. CS was historically defined hemodynamically, with persistent hypotension of systolic blood pressure less than 90 mmHg associated with a severe reduction in cardiac index (less than 1.8L/min/m^2 without support or less than 2.2L/min/m^2 with support), and adequate or elevated filling pressures (left ventricular end-diastolic pressure of greater than 15–18 mmHg) [1]. The Society for Cardiovascular Angiography and Interventions (SCAI) recently updated an expert consensus statement on the classification of CS. The stages range from A, those patients at risk of CS, to E, identifying those patients in extremis. Patients with class C or higher shock are differentiated by evidence of clinical and/or biochemical hypoperfusion [3]. This classification system standardizes the way in which we communicate about CS, provides prognostic valve across AMI- and non-AMI CS cohorts, and allows for better assessment of efficacy of interventions in heterogeneous subsets of CS patients. It is important to recognize the phenotypic variation of CS patients, and how these etiologies can impact outcomes. For example, in the CAPITAL

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Curr Opin Crit Care 2022, 28:419–425
DOI:10.1097/MCC.0000000000000957

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KEY POINTS

- Vasopressor and inotropes remain the mainstay of supportive treatment in CS, despite limited evidence supporting its efficacy and safety in CS.
- Norepinephrine is the preferred vasopressor in CS, but there is no data to support selection of one inotrope over another in CS.
- Inotrope selection should be guided by individual patients' response to therapy and tolerability to potential adverse effects.
- There is an urgent need for randomized trials examining inotropes against placebo in CS.

DOREMI cohort, patients with AMI-CS had significantly higher rates of all-cause mortality, need for MCS device and RRT compared to those with non-AMI-CS, highlighting the need for trials of pharmacologic and device-based interventions in specific subgroups of CS [4▪]. The 2022 SCAI update also included risk factors beyond shock stage that improved mortality risk stratification, allowing for additional subgroup discrimination and improved prognostic utility. A posthoc analysis of the CAPITAL DOREMI trial found that patients with moderate-to-severe or greater valvular stenosis or regurgitation had higher rates of in-hospital mortality [5▪] – whether significant concomitant valve disease is simply a marker of worsened prognosis or a potential therapeutic target is yet to be determined.

The most significant advancement in the care of CS patients has been the SHOCK trial, which showed reduced mortality in AMI-CS with urgent revascularization of culprit coronary artery lesions [6]. Trials to explore other therapeutic interventions, including the intra-aortic balloon pump (IABP) [7] and nitric oxide synthase inhibitors [8] have not shown benefit and the mortality of CS has plateaued at greater than 40% over the last two decades [9]. Accordingly, the mainstay of pharmacologic stabilization remains with vasopressors and inotropes, and these medications are recommended in international guidelines [10,11]. Their use is predominantly based on expert consensus with limited randomized clinical trial data supporting efficacy and safety [12–14]. Here, we review commonly used inotropes, their mechanisms of action and the data surrounding their role in the management of CS.

PHYSIOLOGICAL BASIS OF INOTROPES

The body's adrenergic receptors, divided into alpha and beta receptors, are responsible for performing the functions of the sympathetic nervous system. The alpha-1 receptors are linked to vascular smooth muscle activity, and activation produces systemic vasoconstriction, increasing peripheral vascular resistance and arterial blood pressure. The alpha-2 receptors are located within presynaptic nerve terminals and inhibit the release of endogenous norepinephrine. Activation of beta-1 receptors leads to increased inotropy and chronotropy whereas activation of the beta-2 receptors leads to smooth muscle and vascular relaxation. Most medications used in CS resuscitation have both inotropic and vasopressor properties and take advantage of excitatory and inhibitory effects on the aforementioned receptors to exert their effects on the heart, peripheral vascular system and autonomic nervous system to augment CO and restore end-organ perfusion [15].

NOREPINEPHRINE IS PREFERRED OVER EPINEPHRINE AS FIRST-LINE VASOPRESSOR

The most commonly used vasopressor in CS is norepinephrine, a potent vasopressor acting on alpha-1 adrenergic receptors to cause vasoconstriction and on beta-1 adrenergic receptors in the myocardium, augmenting cardiac contractility [15]. Therapeutic dosing ranges from 0.05 to 1.0 mcg/kg/min [16]. Norepinephrine increases mean arterial pressure (MAP) without an associated increase in heart rate, as outlined in Table 1 [15–17]. This may be due to increased afterload from alpha-1 stimulation causing reflex bradycardia. This proves to be potentially advantageous since tachycardia can worsen myocardial oxygen demand. Furthermore, norepinephrine does not act on the beta-2 adrenergic receptors, preventing the cited epinephrine-induced rise in serum lactate, and allowing lactate to be used as a more reliable marker of end-organ perfusion [18,19].

In contrast, epinephrine has a more potent beta-1 adrenergic effect than norepinephrine, along with moderate beta-2 and alpha-1 adrenergic receptor effects [15]. Therapeutic dosing ranges from 0.1 to 1mcg/kg/min [16]. At lower doses, epinephrine increases CO due to its beta-1 adrenergic inotropic and chronotropic effects, whereas the alpha-1 adrenergic induced vasoconstriction is balanced by the beta-2 adrenergic vasodilation. At higher doses, the alpha-adrenergic receptor effect predominates, resulting in increased systemic vascular resistance (SVR) [20]. Epinephrine is not commonly used as first-line in shock states due to increased risk of tachyarrhythmias, splanchnic vasoconstriction, and hyperlactemia [21]. In a review of several vasopressors and inotropes in CS, only epinephrine was

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Table 1. Commonly used inotropes in CS, with dosing range, receptor binding, hemodynamic effects and adverse effects.

Agent	Therapeutic dosing range	Receptor binding	Hemodynamic effects		Adverse effects
Norepinephrine	0.05–1 μg/kg/min	α1+++ β1++	MAP: ↑ ↑ HR: ↔ or ↓ CO: ↑	+ contractility ++ vasoconstriction	Arrhythmias, Increased pulmonary vascular resistance, peripheral (digital) ischemia
Epinephrine	0.1–1 μg/kg/min	α1+++ β1+++ β2++	MAP: ↑ ↑ HR: ↑ ↑ CO: ↑ ↑	+ contractility ++ vasoconstriction	Ventricular arrhythmias, severe hypertension, cardiac ischemia
Dobutamine	2–20 μg/kg/min	β1++	MAP: ↔ or ↓ HR: ↑ ↑ CO: ↑ ↑	++ contractility + vasodilation	Tachycardia, increased ventricular response rate in patients with atrial fibrillation, ventricular arrhythmias, cardiac ischemia, hypertension, hypotension
Milrinone	0.0625–0.5 μg/kg/min	PDE-3 inhibitor	MAP: ↔ or ↓ HR: ↑ CO: ↑ ↑	++ contractility + vasodilation	Ventricular arrhythmias, hypotension, cardiac ischemia, Torsade des pointes
Levosimendan	0.05–2 μg/kg/min	Calcium Sensitizer	MAP: ↔ or ↓ HR: ↑ ↑ CO: ↑ ↑	++ contractility + vasodilation	Tachycardia, enhanced AV conduction, hypotension

MAP, mean arterial pressure; CO, cardiac output; HR, heart rate. Adapted from Ref. [15–17].

independently associated with profound worsening in cardiac and renal biomarkers and increased 90-day mortality [22]. The advantages of norepinephrine over epinephrine were confirmed in the OptimaCC trial, which randomized 57 patients with AMI-CS to these two agents. Both drugs increased MAP, but epinephrine-treated patients showed higher rates of lactic acidosis, marked and sustained increases in heart rate, and increased cardiac double product – a marker of myocardial oxygen consumption. Although epinephrine is efficacious in increasing MAP, it does so at higher energy costs and lower cardiac efficiency. These effects may be due to the differences in receptor affinity, as only epinephrine acts on beta-2 adrenergic receptors. Most importantly, patients in the epinephrine group had an increased occurrence of refractory shock, but there was no significant difference in mortality between the two groups (60-day mortality of 52% in the epinephrine group and 37% in norepinephrine group). Several limitations must be taken note of in OptimaCC, including the small sample size, lack of clarification regarding maximum dose reached and the short duration of follow-up [23]. Although epinephrine is still often used as a 'push-dose or bolus-dose vasopressor' in peri-arrest situation, sustained infusions for hemodynamic support should be avoided among patients with CS.

SECOND-LINE VASOPRESSORS

Pure vasopressors such as vasopressin or phenylephrine are typically not the first line in CS as they have no effect on cardiac contractility. There are specific situations where a pure vasopressor may be beneficial, such as in afterload-sensitive situations like dynamic left ventricular outflow obstruction (LVOTO) and CS [12]. A vasopressor with inotropic properties like norepinephrine could be detrimental as increasing cardiac contractility would worsen the LVOTO and further compromise forward flow. Additionally, vasopressin may be preferentially selected in patients with marked right ventricular failure since it is thought to increase SVR without an associated increase in pulmonary vascular resistance (PVR), helping to minimize added insult to an already failing RV [24]. This concept is reflected in an RCT where low-dose vasopressin was compared to norepinephrine in patients with milrinone-induced hypotension during CABG. The results found that both drugs effectively restored the milrinone-induced decrease in SVR, but only low-dose vasopressin decreased the PVR/SVR ratio [25]. With regards to pure vasopressor use specifically in CS, the available evidence is experimental in nature with only nonhuman studies published to date. In a pig model of refractory CS complicated by cardiac arrest and resuscitated with veno-arterial ECMO, vasopressin produced quicker lactate clearance, less fluid resuscitation and less pulmonary edema when compared to norepinephrine [26▪]. An ongoing randomized trial (NCT02118467)* is currently investigating phenylephrine and vasopressin versus norepinephrine and epinephrine in ICU patients with shock unresponsive to intravenous fluids, hypothesizing that pure vasopressors will reduce tachyarrhythmias [27▪]. Since the CS population is so diverse and heterogeneous in terms of etiology, these findings

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emphasize the importance of tailoring decisions to individual patient conditions and closely monitoring clinical response.

DOPAMINE IS NOT RECOMMENDED IN CARDIOGENIC SHOCK

Dopamine is another commonly used vasopressor in shock states and acts on beta-1 and alpha-1 adrenergic receptors. Dosing ranges from 2 to 20mcg/kg/min [15]. However, dopamine is not routinely used in CS, with De Backer *et al.* finding increased arrhythmias and 28-day mortality with dopamine compared to norepinephrine in the SOAP II trial [28]. These results were solidified in a recent meta-analysis of randomized control trials (RCT) which concluded that norepinephrine is associated with decreased 28-day mortality, fewer arrhythmic events, and lower incidence of gastrointestinal reactions when compared to dopamine in patients with CS, regardless of etiology [29]. However, questions have been raised regarding the external validity and applicability of the results as the SOAP II trial did not have a standard definition of CS and included obstructive, valvular and postcardiotomy states. The varying hemodynamic profiles may have resulted in treatment-related differences, which were not formally evaluated. As a result, van Diepen *et al.* suggest that the optimal first-line vasopressor agent remains unclear [12] but guidelines support norepinephrine to be the vasopressor of choice due to its efficacy and lower risk of adverse events. Further larger scale and high quality randomized controlled trials are needed to investigate other agents in different phenotypes of CS, and better guide these decisions in an evidence-based manner.

DOBUTAMINE

Dobutamine is one of the most commonly used inotropes in CS. It is a synthetic catecholamine with affinity for beta-1 and beta-2 receptors, and produces positive inotropic and afterload reducing effects [30]. Dosing ranges from 2 to upwards of 20 mcg/kg/min with no need to adjust for renal or hepatic insufficiency [15]. Clinically, dobutamine's short half-life allows the advantage of a 'trial' of inotrope therapy, with rapid assessment of its efficacy and safety [31]. This is particularly important given the lack of robust data showing meaningful benefit with inotropes combined with the signal of established harm, which should temper use until more compelling data is available. A concern with dobutamine, particularly in the post-AMI population, is the purported increase in myocardial oxygen consumption, ischemia and tachyarrhythmias. Among post-AMI patients with severe heart failure, dobutamine was associated with higher supraventricular and ventricular arrhythmic burden compared to enoximone [32]. A retrospective review that included a heterogeneous cohort of CS patients found that arrythmias, particularly sinus tachycardia, were more common in the dobutamine compared to milrinone [33]. Nevertheless, dobutamine is widely used and the combination of dobutamine-norepinephrine is commonly seen in CS patients requiring both vasopressor and inotrope support. A study comparing dobutamine-norepinephrine against epinephrine found that both interventions were similarly effective but epinephrine was associated with more adverse events, including transient lactic acidosis, increased heart rate and arrhythmias, and inadequate gastric perfusion [34].

Lastly, as a beta-adrenergic agonist, concern has been raised about the efficacy of dobutamine with beta-blocker therapy on board. A secondary analysis of CAPITAL DOREMI trial** found no difference in outcomes between dobutamine and milrinone among patients treated with beta-blocker in the 24 h preceding inotrope initiation [35▪▪]. In fact, the beta-blocker cohort demonstrated fewer resuscitated cardiac arrests and deaths, with a trend toward fewer ventricular arrhythmias. There may be a paradoxical protective effect with beta-blocker use, and a dedicated clinical trial would help delineate this finding.

MILRINONE

Milrinone is a positive inotropic agent widely used in patients with end-stage heart failure and CS. Originally approved for use in the 1980s, there is significant experience and comfort with this agent [36]. Milrinone is a phosphodiesterase-3 inhibitor, limiting the breakdown of cyclic adenosine monophosphate (cAMP), increasing activation of protein kinase A, and transporting calcium intracellularly, which ultimately promotes improved contractility [37]. Dosing ranges from 0.0625 to upwards of 0.5 mcg/kg/min, with some clinicians choosing to provide a loading dose at initiation, usually reserved to its intra-operative use. Amongst decompensated heart failure patients, similar steady-state plasma levels and hemodynamic benefits were seen regardless of initial bolus prior to infusion initiation by the 3-h mark. Although the bolus group showed hemodynamic benefits earlier, these patients had more hypotension and tachycardia compared to the infusion alone group [38].

Milrinone has been most extensively studied in the chronic heart failure population, with randomized data demonstrating no differences in morbidity

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or mortality in patients treated with a 48-h milrinone infusion compared to placebo. However, milrinone-treated patients had increased rates of new atrial arrhythmias and sustained hypotension requiring intervention [39]. Interestingly, the authors noted worse outcomes among milrinone-treated patients with ischemic cardiomyopathy compared to nonischemic cardiomyopathy [40] emphasizing the need for dedicated clinicals trials segregated by CS etiology. Lewis *et al.*'s retrospective study comparing milrinone to dobutamine as an initial inotropic medication in CS patients found that these two inotropes had similar effectiveness and safety profiles, but mostly differed in type of adverse events, with dobutamine-treated patients reporting more arrhythmias [33]. Most recently, the CAPITAL DOREMI** trial compared dobutamine and milrinone in SCAI class B-E CS, finding that milrinone was not superior to dobutamine in reducing the composite outcome or any of the individual outcomes, including all-cause in-hospital death, need for new renal replacement therapy, need for cardiac transplant or MCS or resuscitated cardiac arrest. Contrary to retrospective studies previously, there were no significant differences in heart rate, MAP or vasoactive-inotropic score (VIS), which is a measure of cumulative pharmacologic support [41▪▪]. Serial lactate measurements have diagnostic, therapeutic and prognostic value in CS, with recent evidence supporting lactate clearance as a surrogate for in-hospital mortality [42]. A posthoc analysis of the CAPITAL DOREMI trial found that multiple lactate-parameters, as early as 8 h after enrollment, were associated with 30-day mortality, including complete lactate clearance (CLC), percentage lactate clearance and percentage lactate clearance per hour. However, CLC was the strongest predictor of survival at all time points between 8 and 24 h after enrollment [43▪].

LEVOSIMENDAN

Levosimendan is a calcium-sensitizing agent that binds to cardiac troponin C, improving contractility independent of an intracellular rise in calcium [44]. Levosimendan also opens adenosine triphosphate-sensitive potassium channels, resulting in systemic vasodilation [45]. One of the reasons that levosimendan is preferred in CS is that it has minimal effect on the beta-adrenergic receptors [44,46], theoretically reducing myocardial oxygen demand and attenuating risk of tachyarrhythmias. Dosing ranges from 0.05 to 0.2 mcg/kg/min [15]. Although not yet available in North America, the European Society of Cardiology suggests levosimendan, or other phosphodiesterase type III inhibitors, may be preferred as they reduce cardiac filling pressures and in those patients who are on beta-blockers as they act through different physiologic pathways [47]. Levosimendan has been compared to dobutamine in several RCTs but patients have been mostly SCAI class A, and not those with higher severity of shock. These trials have demonstrated improved hemodynamics and reductions in natriuretic peptide levels, but have failed to show meaningful improvements in mortality [48,49]. The results of LevoHeartShock** (NCT04020263), which will compare the early use of levosimendan against placebo in patients with CS treated with vasopressor therapy (first-line therapy being combined norepinephrine-dobutamine), will provide greater insight into its efficacy and safety in this unique patient population [50▪▪].

CONCLUSION

CS continues to carry a high risk of morbidity and mortality. The mainstay of pharmacotherapy lies with vasopressors and inotropes, although dedicated and comparative evidence in the CS population remains sparse. Common inotrope agents include dobutamine, milrinone and levosimendan, each with their own hemodynamic and clinical benefits and risks. The next most urgent question to be answered regarding inotrope therapy is if agents are equally effective, ineffective or harmful. We hope to answer this question with our upcoming trial, CAPITAL DOREMI2, which will randomize SCAI class C/D CS to inotrope or placebo in the initial resuscitation of their shock. Further research is also necessary to determine how inotrope therapy fits into a model of CS with escalating use of MCS. Ultimately, inotrope selection must be guided by physician experience, availability, cost, and most importantly, individual patients' response to therapy.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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An upcoming clinical trial providing the first look at the potential efficacy of levosimendan, a widely used inotrope in heart failure, in the cardiogenic shock population.

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